

# REMARKS

Claims 66 - 88 are pending in the instant application. The Examiner has withdrawn claims 70, 71 and 77 as drawn to the non-elected species. Claim 85 has been amended to insert the word "is" as part of the Markush language of the claim.

In the final office action, the Examiner rejected Applicants' claims 66 - 69, 72, 74, 78, 79, and 82 - 86 under 35 U.S.C. §102(b) as anticipated by Kiesser et al. (US Patent 5,739,091) and claims 75, 76, 80, 81, 87, and 88 under 35 U.S.C. §103(a) as being unpatentable over Kiesser et al. (US Patent 5,739,091). Claims 66 - 69, 72 - 74, 76 and 78 - 86 have been rejected under 35 U.S.C. §103(a) as unpatentable over Scott (EP 272 923), and claims 66 - 69, 72 - 76 and 78 - 88 have been rejected under 35 U.S.C. §103(a) as obvious over Markussen (EP 304 332). Applicants respectfully traverse each of the above-enumerated rejections.

Applicants' claimed granule comprises a seed particle and a matrix surrounding the seed particle. The matrix includes a protein (or enzyme) mixed together with a combination of a sugar or sugar alcohol, and a polysaccharide structuring agent. In one preferred embodiment, as exemplified in example 2, the seed particle is comprised of sodium sulfate crystals and the seed particle is coated with a matrix which is a mixture of a protease enzyme solution in combination with sucrose and starch. The granule is further coated with one or more layers including methylcellulose, titanium dioxide, Neodol and PEG.

As taught in Applicants' disclosure the advantage of mixing the protein with sugar to form an admixture protects the protein from activity loss and attrition. However, sugar has disadvantageous "binder" characteristics so it makes the granule sticky. At page 7, it is stated,

"By burying a protein within a matrix, the protein can be better protected from the twin dangers of attrition and activity loss. However it has not been possible previously to granulate enzymes in sugar or sugar alcohol matrices, since sugars and sugar alcohols exhibit "binder" characteristics, i.e. they are sticky and tend to plaster particles together (as happens intentionally in the case of granulation by agglomeration)."

Also as stated at page 7,

"Surprisingly, it has been found that by the addition of a structuring agent to the sugar matrix formula, protein can be

applied uniformly to individual seed particles at rapid rates without agglomeration or attrition."

The structuring agents, polysaccharides and polypeptide, typically have an anti-tack characteristic which is helpful in reducing the binder characteristic of the sugar or sugar alcohol, and allows the matrix layers to be built up, for example in fluid-bed coating at rapid rates without agglomeration. (see page 8).

With regard to the rejection of the claims under 35 U.S.C. §102(b) as anticipated by Kiesser et al., the Examiner states,

"Kiesser et al. teach enzyme granules. The granules comprise enzyme or enzyme mixture, sugars, such as mono- or disaccharides, and a filler, such as cellulose. See column 1, lines 31 - 39, 60-67, column 2, line 66 to col. 3, line 4. The granules may further comprise binders, such as polyethylene glycol. See col. 2, lines 16 - 24. The granule may be covered with a protective coating (col. 4, lines 5 - 11). The coating can contain sugars (col. 4, lines 8 - 10) or polyethylene glycol (col. 4, line 46). The granules may be prepared by layering the enzyme around dry pre-mix. See col 4, lines 21 - 24."

Even though the Kiesser et al. reference is directed to enzyme granules Applicants contend the claimed invention is not anticipated by Kiesser et al. To anticipate a claim, the reference must contain all of the elements of the claim. See *Hybritech Inc. v Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. Additionally, the reference must disclose all of the claimed elements arranged as in the claim and must sufficiently describe the claimed invention to have placed the public in possession of the invention. The reference must contain an enabling disclosure. *Scripps Clinic & Research Found. v Genentech, Inc.* 18 USPQ2d 1001 (Fed. Cir. 1991).

The construction of Applicants' enzyme granule is fundamentally different than the enzyme granule taught by Kiesser et al. Applicants' granule is a multi-layered granule including a protein matrix surrounding a seed particle. Kiesser et al. do not teach or disclose a granule having a seed particle surrounded by a matrix. Kiesser et al. is directed to an extrudable granule which includes an enzyme. The Examiner states, "The granules may be prepared by layering the enzyme around dry pre-mix. See col 4, lines 21 - 24." However, the disclosure specifically states at col. 4, lines 21 - 27, "The

process is expediently carried out by a procedure in which the enzyme concentrate is added to a previously prepared dry pre-mix of the other pulverulent constituents of the recipe in a suitable mixing apparatus, for example a cone mixer or plough lathe mixer. Water is then metered in to the extent that a composition which can be easily shaped and extruded is formed." Further it is disclosed, "The extrudable composition thus obtained is mixed in the mixture until homogenous and then passed to an extruder." Applicants assert this is not a layering of enzyme.

Applicants argue not only are the granules fundamentally structurally different but also the protein matrix of Applicants' granule is not anticipated by the components disclosed in Kiesser et al. There is nothing in the reference that clearly and unequivocally directs those skilled in the art to make the combination of components of Applicants' matrix.

As taught by Kiesser et al. at column 1, lines 34 – 38, the enzyme granules comprise an enzyme or enzyme mixture, a water-insoluble filler mixture, water-soluble filler mixtures, binders, if appropriate, other granulating auxiliaries, a formate of an alkali metal or alkaline earth metal and if appropriate reducing sugars. The nexus of the invention is the inclusion of a formate of an alkali metal or alkaline earth metal as part of the granule and the addition of a reducing sugar for stabilization of the formate. Particularly preferred are calcium formate and sodium formate.

Water-insoluble fillers include cellulose, starch, cereal flour and the like (polysaccharides). However, as stated at column 2, lines 56 – 63 of the reference, the enzyme granules usually comprise a mixture of cellulose and a laminar silicate or silicate mixture, if appropriate cereal flour and /or starch also being other constituents.

Water-soluble filler mixtures include inorganic water-soluble salts. There is no disclosure of a sugar as a water-soluble filler.

All of the listed binders are polymers and include polyethylene glycol and polyvinylpyrrolidone. The granule may comprise up to 30% binder. There are no sugars listed as binders. The reference teaches "if" reducing sugars are to be used they include monosaccharides (glucose) disaccharides (lactose/maltose), and polysaccharides (dextrins). These reducing sugars are taught to be used for synergistic intensification of the stabilizing action of the formate. At column 3, lines 42 – 45, it is taught that the enzyme granule can comprise 0.5 to 15% by weight of a formate and if appropriate 0.5 to 20% by weight of reducing sugar. There is no teaching that sugar and particularly

sucrose which is not a reducing sugar could be used in a matrix as claimed by Applicants.

As stated at col. 5, lines 12 - 15 of the reference,

"The enzymes in the granules according to the invention are stabilized in a surprising manner by incorporation of a formate of an alkali metal or alkaline earth metal, if appropriate in combination with a reducing sugar."

There is no clear and unequivocal teaching in the reference that a protein matrix is comprised of a protein or enzyme mixed together with a combination of a sugar and polysaccharide structuring agent. It is the particular combination of the components of the matrix which circumvent the problem of agglomeration.

Applicants also assert that the invention is not made obvious by the teaching of Kiesser et al. There is no suggestion or motivation provided by Kiesser et al. to make multi-layered enzyme granules. Additionally, the Kiesser et al. reference must include a suggestion or provide a motivation to modify the components of the enzyme mixture in a manner claimed by the Applicants. While some components of Applicants' multi-layered granule may arguably be found in the Kiesser et al. disclosure even with selectively picking and choosing one skilled in the art would not know which specific components would comprise the instant invention.

Beyond looking to the reference to determine if it suggests doing what the inventor has done, one must also consider if the reference provides the required expectation of succeeding in that endeavor. Both, the suggestion and the expectation of success must be found in the prior art reference and not Applicants' disclosure.

There is no suggestion to make a multi-layered granule according to the instant invention, and further there is no guidance provided in the reference to provide an enzyme or enzyme mixture admixed with a combination of a sugar (particularly sucrose) and a polysaccharide structuring agent (particularly starch) to produce a coating layer surrounding a seed particle.

The Examiner has also rejected claims 75, 76, 80, 81, 87 and 88 as unpatentable over Kiesser et al. and argues,

"The reference does not teach all particular enzymes and all particular cellulose-derived fillers as instantly claimed. Selection of particular enzymes would be prima facie obvious as the reference teaches enzyme granules in general and is not limited to any

particular enzyme. As for selection of filler, as cellulose derivatives are well known to be used for this purpose, selection of a particular cellulose derivative would be obvious for an artisan to be achieved in a way of optimization."

As argued above, Applicants' enzyme granule is structurally different than the enzyme granule of Kiesser et al. and therefore dependent claims 75, 76, 80, 81, 87 and 88 are not unpatentable over the reference. Moreover, Applicants contend while numerous filler compounds may have been known in the art to use in constructing enzyme granules, the Kiesser et al. reference merely listed cellulose as one of many water-insoluble fillers. As taught at col. 2, the water-insoluble filler according to the invention usually comprises a mixture of cellulose and a laminar silicate or laminate silicate mixture, if appropriate cereal-flour and/or starch. As listed in the examples the water-insoluble components include cellulose, kaolin, calcium carbonate, bentonite, wheat flour and starch.

With respect to the rejection over Scott, the Examiner states, "Scott teaches granules including enzyme (glucose oxidase), sugar (glucose) and low molecular weight polysaccharides (e.g. cellulose) and optionally synthetic polymer. The reference does not teach forming a granule over a seed particle and the presence of a coating layer over the granule.. " However, it is the Examiner's position if there are any differences between Applicants' claimed granule and that of the prior art, the differences would appear to be minor in nature.

As acknowledged by the Examiner, Scott does not teach or suggest a multi-layered granule. The Scott reference is concerned with solving a particular problem: the addition of oxygen scavenging food ingredients to prevent oxygen deterioration in food products. This problem is solved in two specific ways. The first provides a dry free flowing particulate preparation which is an effective oxygen scavenger containing glucose (sugar) and glucose oxidase (enzyme). This is referred to as a single enzyme system. The second provides a dry free flowing particulate preparation which is an effective oxygen scavenger containing glucose oxidase (enzyme), a low molecular weight polysaccharide (maltodextrin) and a hydrolytic enzyme capable of catalyzing the hydrolysis of the polysaccharide into glucose units. This is referred to as double enzyme system.

In the first system the glucose and glucose oxidase are combined to form an admixture. This system while including an enzyme and a sugar is devoid of teaching an admixture of a polysaccharide structuring agent mixed with the sugar and enzyme. In the second system the enzyme glucose oxidase is combined with a low weight polysaccharide and a second enzyme wherein the second enzyme can catalyze the hydrolysis of the polysaccharide into glucose units. This system while including an enzyme and a polysaccharide is devoid of teaching an admixture of a sugar mixed with the enzyme and polysaccharide. Applicants' multi-layer enzyme granulate is not made obvious by the particulate enzyme composition as disclosed by Scott. The reference particles do not suggest either explicitly or implicitly the instantly claimed granules wherein an enzyme is admixed with a combination of a sugar or sugar alcohol and a polysaccharide structuring agent.

The Examiner has also rejected Applicants' claims as unpatentable over Markussen (EP 304332). The Examiner states,

"Markussen teaches enzyme granules comprising an enzyme core surrounded by a coating comprising cellulose or artificial binders. The granules further comprises a binder such as polyvinyl pyrrolidone cellulose derivatives, etc., and a granulating agent, such as polyglycols. .. The reference granule does not contain sugar and polysaccharide. However, addition of such ingredients would be prima facie obvious when the enzyme granulates are to be used as nutrient additives because the reference teaches that in such cases the core could contain sugar or starch or protein. See p. 2, lines 32 - 34."

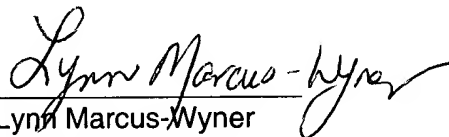
Applicants granule is different from and unobvious over Markussen. Applicants core is an inert particle and the layer surrounding the inert particle is an admixture of the enzyme, sugar and polysaccharide structuring agent. In one embodiment, Markussen teaches a core having a protein in the core and a coating either with or without a protein. In another embodiment, the core does not have a protein but a coating which includes cellulose fibers or artificial fibers, a binder, a filler, one or more granulating agents and an enzyme. The binders are disclosed as polymer compounds. There is no teaching of admixing the enzyme, sugar and polysaccharide compound. The fact that the core could include a sugar, starch or protein is not a disclosure sufficient to teach or suggest a

coating layer around a seed particle wherein the coating layer is a matrix comprising a mixture of a protein, sugar and polysaccharide structuring agent.

Applicants contend instant claims 66 – 88 are patentable over the cited references, and withdrawal of all pending rejections is respectfully requested. Allowance of the claims is kindly solicited. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 846-7620.

Respectfully submitted,

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Enclosure: Marked-up version of amended claim

**MARKED-UP VERSION OF CLAIMS**

85.(Amended) The granule of claim 83, wherein said sugar is selected from the group consisting of glucose, fructose, raffinose, maltose, lactose, trehalose and sucrose.